REMARKS

With entry of the present amendment, claims 1-32 and 34-40 are pending. Claims 1-29 and 40 are allowed. Claim 33 is canceled. Claims 9, 18, 20, 21, 27, 29, 31, 34 and 37 are amended. Claims 41-43 are withdrawn.

Entry of this amendment and reconsideration of the claims, as amended and in view of the following remarks, is requested.

The specification is amended at several locations indicated above to replace "lambda*6*" or "lambda*4*" with "λ^6" or "λ^4."

Claims 9, 18, 20, 21, 27 and 29 are also amended to replace "lambda*6*" or "lambda*4*" with "λ^6" or "λ^4."

Claim 31 is amended to delete "the general" before "formula."

Claim 34 is amended to replace "protected amine" with "protected ammonia" immediately below formula II, and to replace "protecting group L" in step (b) with "any optional protecting group from the resulting compound of step (a)."

Claim 36 is amended to correct the spelling of "catalyzed."

Claim 37 is amended to correct the spelling of "comprising converting."

No new matter is believed to be presented by the foregoing amendments.

The Restriction Requirement

The application is subject to restriction as follows:

Group I: Claims 1-40, directed to compounds and compositions.

Group II: Claims 41-43, directed to methods of treatment using the compounds of Group I.

Applicants confirm their election of Group I, claims 1-40, for substantive prosecution in the instant application. Applicants' election is without prejudice to their right to pursue the subject matter of non-elected claims 41-43 either in the instant application or a divisional application.

Claims 41-43 are stand withdrawn from consideration, but are not cancelled. Applicants request that rejoinder of these claims be considered when and if the compound claims of Group I are allowed.

Claim Objections Due to Informalities

Claims 9, 14, 18, 21, 27 and 29 are objected due to the appearance of "lambda*6*" in the chemical name. This rejection is overcome.

As respects claim 14, applicants believe the inclusion of this claim in this objection was in error as the term "lambda" does not appear in this claim.

The Examiner queries if "-6-"was intended instead of "lambda*6*." Actually, the term "λ^6" was intended as applicants are using the Lambda Convention of IUPAC nomenclature. A copy of the "Treatment of Variable Valence in Organic Nomenclature (λ Convention)" is enclosed herein for the Examiner's convenience. The use of the Greek letter "λ" is acceptable in chemical names to designate non-standard (or variable) valence states of heteroatoms in organic nomenclature. Apparently the spelling of "lambda" and the "*6*" instead of using the Greek symbol with superscripts was an artifact of the autonom function of the ISIS Draw software used to name some of the compounds. Applicants have revised the specification (except the table at pp. 34-36) and claims to state "$\lambda^{\#}$" instead of "lambda*#*." This objection is thus believed to be overcome.

The Section 112 Rejections

Claim 30 is rejected under 35 USC § 112, second paragraph, as being indefinite due to the use of the clause "an optionally protected NH_2 group" in the definition of substituent X. It is asserted that one skilled in the art would not know which protecting group to use because the conditions against which the amino group is protected are not specified. This rejection is traversed.

Claim 30 is directed to compounds of formula A-1-I, which are intermediates useful in the synthesis of the compounds of formula I, claim 1. Substituent X is defined as being "NO_2 or an optionally protected NH_2 group."

As is provided in paragraph [0082], page 29, of the instant application, one skilled in the art would know which NH_2 (or amino) protecting group to use in a specific chemical reaction. That is what the definition of a "skilled artisan" is in this context. Precisely as the Examiner notes on page 6 of the Office Action ("OA"), some groups are known to be stable in base and others in acid. Applicants do not have to specify these details in the application. A skilled artisan would know which groups to pick depending on the conditions of each reaction intended. As such, applicants need not provide these details. It is well settled that a patentee need not include and "preferably omits from the disclosure any routine technology that is well known at the time of application." *Chiron Corp. v. Genentech*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004).

In support of applicants' position that the term "amino (or NH_2) protecting group" is well-known in the art or organic synthesis, applicants submit a copy of the table of contents for Chapter 7, "Protection for the Amino Group" from Protective Groups I Organic Synthesis by Theodora W. Green, pp. 218-22, (John Wiley & Sons, 1981). Applicants also note that this term appears in the claims of many issued patents (588 patents for the 25 year period up to 1981). Finally, applicants enclose a copy of the Board of Patent Appeals decision in *Ex parte Peter Karl Matzinger et al*, Appeal No.

2003-2146, where this issue was considered by the Board and decided in the applicants' favor. While this decision is noted as not being binding precedent, it certainly supports applicants' understanding of the law applicable to the very facts herein presented.

For the foregoing reasons, the rejection of claim 30 under 35 USC § 112, second paragraph, is legally improper and should be withdrawn.

Claims 31-33 are also rejected under 35 USC § 112, second paragraph, as being indefinite for use of the phrase "general formula" immediately above formula (III) in claim 31. As suggested by the Examiner, claim 31 is amended to delete the word "general" and this rejection is thus overcome.

Claim 31 is rejected under 35 USC § 112, second paragraph, additionally for use of the expression "L signifies a leaving group" in claim 31. This rejection is traversed.

Applicants concur with the Examiner that a "leaving group" may be different depending on the molecule to which it is attached and the conditions of the reaction in which the group is to be cleaved. However, that does not render the term indefinite. As with the term "amino protecting group," the term "a leaving group" is well-known in the art or organic synthesis. A leaving group is a well known class of materials, all of whose members, and which members to use under which conditions, would be recognizable to one skilled in the art . As a demonstration of this, a search conducted in the UPTO's Website for issued patents whose claims contain the term "leaving group" yielded 2,912 such patents that issued from 1976 to the present. A copy of the first page of the results is attached. In addition, a Google search of the phrase "leaving groups organic synthesis" yielded 1,410,000 hits. The fist ten are enclosed. As is demonstrated just by these first ten hits, many scholarly articles and Organic Chemistry texts use the term "leaving group." For example, enclosed is the Table of Contents for Side Reaction in Organic Synthesis, Florencio Zaragoza Dorwald (Wiley-VCH 2004). The Examiner's

attention is directed to Chapter 4.2 which is entitled "Structure of the Leaving Group." Also enclosed is the ten page text of an Organic Chemistry Lecture given at the University of Maine, available on the Internet, using this term. *See* in particular page 6. There is no doubt on the current record that a "leaving group" is an art recognized term and as such no specific definition is required in applicants' specification or claims. This term is definite and the rejection under Section 112 should be withdrawn.

Claim 33 is rejected under 35 USC § 112, second paragraph, as the phrase "deprotecting a protected hydroxy or protected amino group" in lines 1 and 2 are deemed to lack antecedent basis. This claim is canceled.

Claims 34-39 are also rejected under 35 USC § 112, second paragraph, as being indefinite for referring to "a protected amine." As suggested by the Examiner, claim 34 is amended to refer to "protected ammonia" instead. Thus, this rejection is thus overcome.

Claims 34-39 are additionally rejected under 35 USC § 112, second paragraph, as being indefinite for use of "cleaving the protecting group L." As suggested by the Examiner, claim 34 is amended to state "cleaving any optional protecting group from the resulting product of step (a)." This rejection is believed to be overcome.

Claims 34-39 are also rejected because the definition of L and L' in the penultimate line as "a leaving group" is asserted to be indefinite. For the reasons stated above, the term "a leaving group" is well understood in the art is thus not indefinite. This rejection is traversed for the reasons herein of record.

For the foregoing reasons, the rejections under Section 112, second paragraph, are traversed or overcome and should be withdrawn.

CONCLUSION

The foregoing amendment is fully responsive to the Office Action issued October 11, 2005. Applicants submit that all pending claims, as amended, are allowable. Early and favorable consideration is earnestly solicited.

If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application which may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney is respectfully solicited.

Applicants believe that no fee is due with this communication. However, should the Patent Office determine that a fee is owed, or a credit is due to applicant, the Patent Office is hereby authorized to charge any required fees, including any extension of time and/or excess claim fees, or credit any overpayment, to applicant's Deposit Account 08-2525 as appropriate.

Respectfully submitted,

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Attachments

170267

International Union of Pure and Applied Chemistry
Organic Chemistry Division
Commission on Nomenclature of Organic Chemistry

TREATMENT OF VARIABLE VALENCE IN ORGANIC NOMENCLATURE (λ CONVENTION)

Recommendations 1983

Prepared for publication by W. H. Powell and published in *Pure Appl. Chem.*, 1984, **56**, 769-778.

http://www.chem.qmul.ac.uk/iupac/hetero/Lm.html

World Wide Web version prepared by G. P. Moss

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See also *Chem. Listy*, 1985, **79** 1281-1286. (in Czech); F C Alderweireldt, H J T Bos, L Maat and D Tavernier, *Regels voor de nomenclatuur van de organische chemie, sectie D, lambda-conventie, delta-conventie*, Koninklijke Nederlandse Chemische Vereniging, Koninklijke Vlaamse Chemische Vereniging, 1990, ISBN 90-71446-04-2 (in Dutch) and *Wiad. Chem.*, 1989, **43** 93-102 (in Polish).

For problems in converting the text into a World Wide Web version see the IUPAC home page.

Any comments, corrections or suggestions for a future edition should be e-mailed to g.p.moss@qmul.ac.uk

Important Note: This version is formatted using the font symbol for Greek letters. If you cannot see a Delta (a triangle) in quotation marks next "Δ" click here for a version where Greek letters are created using graphic images.

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REFERENCES

Continued with Lambda Convention Introduction

Return to IUPAC Chemical Nomenclature home page.

TREATMENT OF VARIABLE VALENCE IN ORGANIC NOMENCLATURE (λ CONVENTION)

Recommendations 1983

CONTENTS

RECOMMENDATIONS

The extension of substitutive nomenclature to compounds containing heteroatoms of variable valence requires a method for distinguishing between the various valence states of each atom. These recommendations, designated by Lm (lambda), provide a general method for indicating nonstandard valence states of formally neutral skeletal atoms in parent hydrides (but see Note).

> *Note.* Cyclic parent hydrides having cumulative double bonds in addition to the maximum number of noncumulative double bonds in the rest of the structure will be included in a forthcoming comprehensive treatment of cumulative double bond systems.

Lm-1.0. Terminology

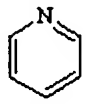
Lm-1.1. Bonding Number

The *bonding number*, "n", of a skeletal atom in a parent hydride is the sum of the total number of valence bonds to adjacent skeletal atoms, if any, and the number of attached hydrogen atoms. The relevance of these recommendations to naming radicals and ions is not considered in this report.

Examples:

1. SH_2 n = 2
2. SnH_2 n = 2
3. NH_2-NH_2 n = 3

4. PH_4-NH-PH_4 N, n = 3; P, n = 5

5.  N, n = 3; C, n = 4

6. SiH_2=SiH_2 n = 4

7. SH_6 n = 6

8. IH_7 n = 7

Lm-1.2. Standard Bonding Number

The *bonding number* of a neutral atom in a parent hydride is *standard* when it has the value given in the following table of elements that occur more or less frequently in organic compounds. It is nonstandard when its value is either larger or smaller.

Bonding number	3	4	3	2	1
	B	C	N	O	F
		Si	P	S	Cl
		Ge	As	Se	Br
		Sn	Sb	Te	I
		Pb	Bi	Po	At

Lm-2.0. Designation of Nonstandard Bonding Numbers

A nonstandard bonding number of a *neutral* skeletal atom in a *parent hydride* is indicated by the symbol λ^n, where n is the bonding number as defined in Lm-1.1.

If the locant for an atom with a nonstandard bonding number is used in the name of the normal (standard) parent hydride, the λ^n symbol is cited immediately after this locant. If the locant for such an atom is *not* expressed in the name, the locant, if necessary and the λ^n symbol are cited in front of the name of the parent hydride, but after any indicated hydrogen (see Lm-3.0).

Numbering of parent hydrides with heteroatoms in nonstandard valence states follows the rules of Sections B and C of the IUPAC Organic Nomenclature Rules (Ref. 1) for numbering heteroatoms as far as possible. When a choice is needed between the same skeletal atom in different valence states, the one in a nonstandard valence state is preferred for assignment of the lower locant. If a further choice is needed between the same skeletal atom in two or more nonstandard valence states, preference for lower locant is given in order of the decreasing numerical value of the bonding number, i.e., λ^6 is preferred to λ^4.

Examples:

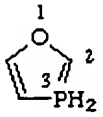
1. SH_4 λ^4-Sulphane [the name sulfurane has been suggested (Ref. 7)]

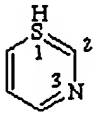
2. λ^5-Iodane [the name periodinane has been suggested (Ref. 8)]

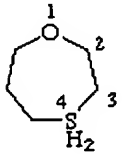
IH_5

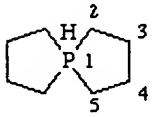
3. $HS-SH_4-SH$ (1 2 3) — 2λ⁶-Trisulfane

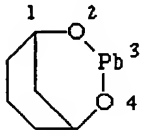
4. $H_4P-PH_3-PH_4$ (1 2 3) — 1λ⁵,2λ⁵,3λ⁵-Triphosphane (not Tri-λ⁵-phosphane. An abbreviated form $(\lambda^5)_3$-triphosphane (in speech tri-λ⁵-triphosphane is perhaps better) is permissible.)

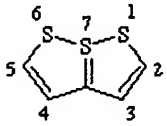
5.  — 1,3λ⁵-Oxaphosphole

6.  — 1λ⁴,3-Thiazine

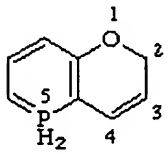
7.  — 1,4λ⁴-Oxathiepane

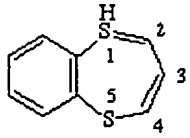
8.  — 5λ⁵-Phosphaspiro[4.4]nonane

9.  — 2,4-Dioxa-3λ²-plumbabicyclo[3.3.1]nonane

10.  — 7λ⁴-[1,2]Dithiolo[1,5-*b*][1,2]dithiole or 1,6,6aλ⁴-Trithiapentalene

Note: Nonstandard valence states in fused ring systems are indicated only in the complete ring system, not in component rings.

11.  — 2*H*-5λ⁵-phosphinino[3,2-*b*]pyran

12.  — 1λ⁴,5-Benzodithiepin (the λ⁴ sulfur atom is preferred for lowest locants)

Lm-3.0. Indicated Hydrogen.

Lm-3.1. Maximum Number of Noncumulative Double Bonds

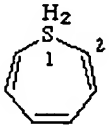
When the maximum number of noncumulative double bonds is assigned to a parent ring structure, account must be taken of the modified valence of ring atoms with nonstandard bonding numbers.

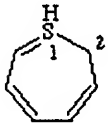
Lm-3.2. Indicated Hydrogen Symbolism.

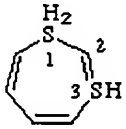
After the maximum number of noncumulative double bonds has been assigned according to Rule Lm-3.1, any ring atom with a bonding number of three or higher connected to adjacent ring atoms by single bonds only, and carrying one or more hydrogen atoms, is designated by the "indicated hydrogen" symbolism as described in Rule A-21.6 (Ref. 1). If the preceding rules leave a choice, such ring atoms are preferred for low locants.

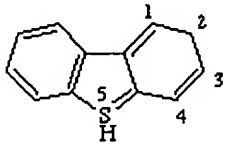
> *Note*: Designation of indicated hydrogen at nonbridgehead ring positions between two bivalent ring atoms is often omitted.

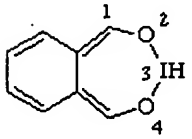
Examples:

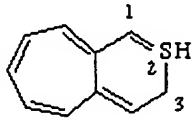
1.  1*H*-1λ⁴-Thiepine

2.  2*H*-1λ⁴-Thiepine

3.  1*H*-1λ⁴,3λ4-Dithiepine (the -SH_2- λ⁴-sulfur atom is preferred for low numbering)

4.  2*H*-5λ⁴-Dibenzothiophene

5.  3*H*-3λ⁴,2,4-Benziodadioxepin

6.  3*H*-2λ⁴-Cyclohepta[*c*]thiopyran (not 2*H*-3λ⁴-cyclohepta[*c*]thiopyran)

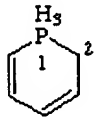
Lm-4.0. Derivatives of Parent hydrides

Derivatives of *parent hydrides* with skeletal atoms in nonstandard valence states are named according to the established rules of organic nomenclature (Ref. 1) as exemplified below.

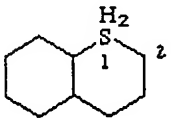
Lm-4.1. Saturation of Double Bonds

Saturation of *double bonds* in a ring system whose parent name requires the maximum number of noncumulative double bonds is indicated by hydro prefixes as prescribed by Rules A-23.1 and B-1.2 (Ref. 1).

Examples:

1. 

1,2-Dihydro-1λ^5-phosphinine

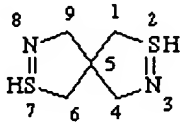
2. 

Decahydro-1λ^4-benzothiopyran

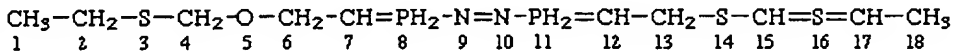
Lm-4.2. Multiple Bonds with a Saturated Parent Hydride

The presence of *multiple bonds* in a parent hydride whose parent name requires saturated skeletal atoms at all positions, is described by subtractive suffixes such as "ene" and "yne" (see Rules A-3, A-11.3, A-31.2, A-41.3 in Ref.1).

Examples:

1. 

2λ^4,7λ^4-Dithia-3,8-diazaspirol4.4]nona-2,7-diene

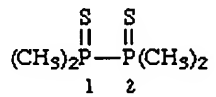
2. 

5-Oxa-3,14,16λ^4-trithia-9,10-diaza-8λ^5,11λ^5-diphosphaoctadeca-7,9,11,15,16-pentaene

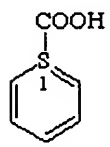
Lm-4.3. Derivatives

Derivatives formed by *substitution* of *hydrogen atoms* of the parent hydride are named by means of prefixes and/or suffixes in the established manner (Rule C-0.1, Ref. 1).

Examples:

1. 

1,1,2,2-Tetramethyl-1,2-dithioxo-1λ^5,2λ^5-diphosphane

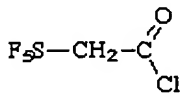
2. 

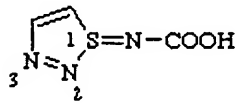
1λ^4-Thiopyran-1-carboxylic acid

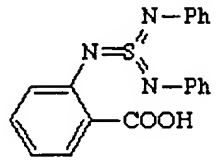
Lm-4.4. Prefixes

Prefixes for describing substituents derived from parent hydrides having heteroatoms in nonstandard valence states are formed in the usual manner by using endings such as "yl", "ylidene", "diyl", etc. (Ref. 1).

Examples:

1.  (Pentafluoro-λ^6 -sulfanyl)acetyl chloride

2.  *N*-(1*H*-1λ^4,2,3-Thiadiazol-1-ylidene)carbamic acid

3.  *N*-[Bis(phenylimino)-λ^6-sulfanylidene]anthranilic acid

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REFERENCES

1. International Union of Pure and Applied Chemistry, *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979.

2. International Union of Pure and Applied Chemistry, The Designation of Nonstandard Classical Valence Bonding in Organic Nomenclature (Provisional), *Pure Appl. Chem.* **54**, 217-227 (1982).

3. International Union of Pure and Applied Chemistry, Revision of the Extended Hantzsch-Widman System of Nomenclature for Heteromonocycles (Recommendations 1982), *Pure Appl. Chem.* **55**, 409-416 (1983).

4. A. F. Clifford, *J. Chem. Doc.* **5**, 91-95 (1965); **10**, 180-185 (1970).

5. International Union of Pure and Applied Chemistry, Nomenclature of Inorganic Chemistry, 2nd Edition, Butterworths, London, 1979, (a) Rule 0.1, p. 5; (b) Rule 1.31, p. 11.

6. International Union of Pure an d Applied Chemistry, Nomenclature of Organic Chemistry, Section D (Tentative), IUPAC Information Bulletin Appendixes on Tentative Nomenclature, Symbols, Units, and Standards, No. 31, August, 1973.

7. J. C. Martin and R. J. Arhart, *J. Am. Chem. Soc.* **93**, 2339-2342 (1971).

8. R. L. Amey and J. C. Martin, *J. Am. Chem. Soc.* **100**, 300-301 (1978).

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PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

THEODORA W. GREENE

Protective Groups in Organic Synthesis

Theodora W. Greene

Harvard University

A Wiley-Interscience Publication

JOHN WILEY & SONS, New York · Chichester · Brisbane · Toronto

Library of Congress Cataloging in Publication Data:

Greene, Theodora W 1931-

Protective groups in organic synthesis.

"A Wiley-Interscience publication."

Includes index.

1. Chemistry, Organic—Synthesis. 2. Protective groups (Chemistry) I. Title. [DNLM: 1. Chemistry, Organic. QD 262 G812p]

QD262.G665 547'.2 80-25348

ISBN 0-471-05764-9

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

中華民國七十一年 月初版

發行所：國興出版社

發行人：楊國藩

新竹市西門街262號

電話：(035) 223129號

行政院新聞局局版台業字第0465號

總經銷：黎明書店

新竹市中正路72號

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郵政劃撥七〇二七三號

實價：200元

2

Protection for the Hydroxyl Group Including 1,2- and 1,3-Diols

*Included in Reactivity Chart 1.

**Included in Reactivity Chart 2.

**Included in Reactivity Chart 2.

Hydroxyl groups are present in a number of compounds of biological and synthetic interest including nucleosides, carbohydrates, steroids, and the side chain of some amino acids. During oxidation, acylation, halogenation with phosphorus or hydrogen halides, or dehydration reactions of these compounds, a hydroxyl group must be protected. Ethers, acetals and ketals (cleaved by mild acidic hydrolysis), and esters (cleaved by basic hydrolysis) can be prepared to protect isolated hydroxyl groups; 1,2- and 1,3-diols can be protected as cyclic ethers (e.g., acetonides), cleaved by acidic hydrolysis, and as cyclic esters (e.g., carbonates and boronates), cleaved by basic hydrolysis. Simple *n*-alkyl ethers are stable compounds that are resistant to mild cleavage conditions. Benzyl and benzyl-

***Included in Reactivity Chart 3.

7

Protection for The Amino Group

*Included in Reactivity Chart 8.

**Included in Reactivity Chart 9.

***Included in Reactivity Chart 10.

***Included in Reactivity Chart 10.

A great many protective groups have been developed for the amino group, including carbamates (>NCO$_2$R), used for the protection of amino acids in peptide and protein syntheses, and amides (>NCOR), used more widely in syntheses of alkaloids and for the protection[a] of the nitrogen bases adenine, cytosine, and guanine in nucleotide syntheses.

Carbamates are formed by reaction of an amine with an azido- or chloroformate or with a carbonate; amides are formed from the acid chloride. *n*-Alkyl carbamates are cleaved by acid-catalyzed hydrolysis; *N*-alkylamides are cleaved by acidic or basic hydrolysis at reflux, and by ammonolysis, conditions that cleave peptide bonds.

In this chapter detailed information is provided for the most useful protective groups (in general these are included in Reactivity Charts 8–10); structures and references are given for protective groups that seem to have more limited use. The conventions that are used in this chapter are described on p. xii.[b]

[a] C. B. Reese, *Tetrahedron*, 34, 3143 (1978); V. Amarnath and A. D. Broom, *Chem. Rev.*, 77, 183

Paper No. 22

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte PETER KARL MATZINGER, MICHELANGELO SCALONE and ULRICH ZUTTER

Appeal No. 2003-2146
Application No. 09/546,143[1]

ON BRIEF[2]

Before WINTERS, SCHEINER, and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 12, 14, 15, 17, 19, 21, 23 and 25. Notwithstanding appellants indication (Brief, page 2) that no claims have been cancelled, claims 1-9 are cancelled. See Paper No. 2, page 2. Of the remaining pending claims, the examiner has:

- objected to claims 13, 16, 18, 20, 22 and 24 as being dependent upon a rejected base claim, but would be allowable if rewritten in

[1] The instant application is a divisional of Application No. 09/195,512, filed Apr. 3, 1997, now U.S. Patent No. 5,902,882, issued May 11, 1999, which is a continuation of Application No. 08/832,253, filed Nov. 19, 1998, now U.S. Patent No. 6,069,245, issued May 30, 2000.

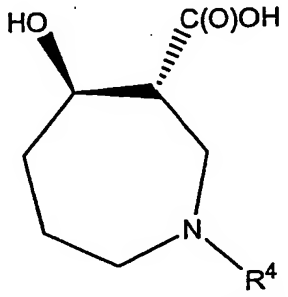
[2] In accordance with 37 CFR 1.194(c), the Board decided that an oral hearing was not necessary in this appeal.

independent form (See Paper No. 3, page 6 and Paper No. 9, page 4); and

- indicated that claims 10, 11 and 27 are allowable (See Paper No. 3, page 7, and Paper No. 9, page 4).

Claims 12, 17, 23 and 25 are illustrative of the subject matter on appeal and are reproduced below:

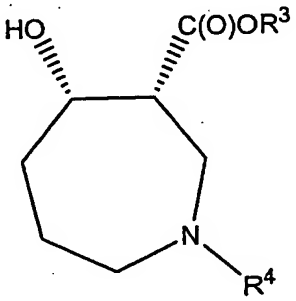
12. A compound selected from the group consisting of compounds of the formula



V[,]

wherein R^4 is an amino-protecting group.

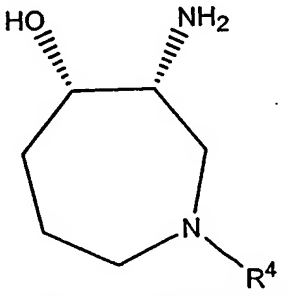
17. A compound selected from the group consisting of compounds of the formula



VIII,

wherein R^3 is lower alkyl and R^4 is an amino-protecting group, in the absence of substantial amounts of other enantiomers of the compound.

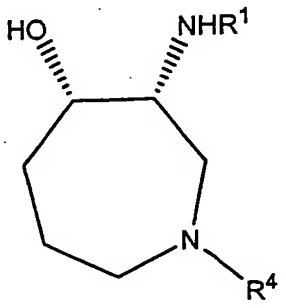
23. A compound selected from the group consisting of compounds of the formula



X,

wherein R^4 is an amino-protecting group.

25. A compound selected from the group consisting of compounds of the formula



XI,

wherein R^1 is an acyl residue of an aromatic carboxylic acid and R^4 is an amino protecting group.

The references relied upon by the examiner are:

Barbier et al. (Barbier) 5,583,222 Dec. 10, 1996
(102(e) date Jan. 4, 1995)

Adams et al. (Adams), "Total synthesis of balanol: a potent protein kinase C inhibitor of fungal origin," J. Chem. Soc. Perkin Trans. I, pp. 2355-62 (1975)

Krogsgaard-Larsen et al. (Krogsgaard-Larsen), "Inhibitors of GABA Uptake. Syntheses and 1H NMR Spectroscopic Investigations of Guvacine, (3RS, 4SR)-4-Hydroxypiperidine-3-carboxylic Acid, and Related Compounds," Acta Chemica Scandinavica B, Vol. 32, pp. 327-34 (1978)

L. G. Wade, Jr. (Wade), Organic Chemistry 103 and 115 (Prentice-Hall, Inc., 1987)

GROUND OF REJECTION

Claims 12, 14, 15, 17, 19, 21, 23 and 25 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of the phrase "amino protecting group."

Claims 12, 14, 15, 17, 19, 21, 23 and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as based on a disclosure that fails to enable the full scope of the claimed invention.

Claim 17 stands rejected under 35 U.S.C. § 102(b) as anticipated by Krogsgaard-Larsen.

Claims 23 and 25 stand rejected under 35 U.S.C. § 102(b) as anticipated by Adams.

Claim 25 stands rejected under 35 U.S.C. § 102(e) as anticipated by Barbier.

Claims 25 and 26 stand rejected under 35 U.S.C. § 103 as being unpatentable over Barbier.

We reverse.

DISCUSSION

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

The claims are directed to a compound selected from the group consisting of compounds of a specified formula wherein one of the substituents, R^4, set forth in the specified formula is an amino-protecting group. According to the examiner (Answer, page 4), the "claims recite the limitation of 'amino protecting group' which has no description in the specification other than 'tert.-butoxycarbonyl' as a sole representative of said group. Thus, one skilled in the art cannot ascertain what other groups can be considered as an 'amino[-]protecting group'." We note, however, while the examiner asserts (id.) that the specification describes "tert.-butoxycarbonyl" as a sole representative of an "amino-protecting group," the examiner later finds (Answer, bridging sentence, pages 4-5), the specification provides an enabling description of tert-

butyl ester, tert-butyl carboxylate, and tert-butoxycarbonyl as amino-protecting groups within the scope of R^4 as set forth in appellants' claimed invention.

For their part, appellants assert (Brief, page 4), "[t]he term 'amino-protecting group', as used in the rejected claims, is well-known in the art to which this invention belongs, organic synthesis." In support of this assertion appellants rely on the table of contents to chapter 7 of Green[3] to demonstrate that "'amino protecting groups' are well-known and exemplified by many members, all of which are within the skill of the art of organic synthesis." We find it noteworthy to mention that the title of this chapter (chapter 7) of Green is "Protection for The Amino Group."

In response, the examiner argues (Answer, page 7, emphasis removed), "it is still unclear whether the scope of 'amino protecting group' includes groups cited by Green, or goes beyond that." The examiner makes a similar argument (id.) with respect to appellants' assertion (Brief, page 4) that other patents have issued "with the term 'amino protecting groups' in the claims." On consideration of the record before us, we agree with appellants that the phrase "amino protecting group" is a term of art. Accordingly, we disagree with the examiner's conclusion that the phrase is indefinite to those of skill in the art.

As set forth in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir. 1991):

> The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A

[3] Theodora W. Greene (Green), Protective Groups in Organic Synthesis, pp. 218-22, Table of Contents to Chapter 7, "Protection for The Amino Group" (John Wiley and Sons, 1981).

> decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. See Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits.").

Furthermore, claim language must be analyzed "not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971). Whether a claim is indefinite under 35 USC § 112, second paragraph, depends upon whether those skilled in the art would understand what is claimed, or the scope or the bounds of the claim, when read in light of the specification. The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning of indefiniteness.

Accordingly, we disagree with the examiner's assertion (Answer, page 7) that "[t]he issue of indefiniteness is not whether one skilled in the art can understand a term (or terms), rather it is the metes and bounds of the invention." As set forth in Amgen, a decision as to whether a claim is invalid under 35 U.S.C § 112, second paragraph, requires a determination as to whether those skilled in the art would understand what is claimed. Based on the examiner's assertion (Answer, page 7), and the evidence of record, it appears that there is no dispute that a person of ordinary skill in the art would understand what is claimed. Instead, it appears that the examiner is concerned solely with the breadth of the

claimed invention. In this regard, we would agree with the examiner that the scope of the claim is extremely broad. However, as the examiner recognizes (Answer, page 7), "breadth is not indefiniteness...." In re Miller, 441 F.2d 689, 693, 169 USPQ 597, 600 (CCPA 1971) ("[B]readth is not to be equated with indefiniteness.").

In our opinion, when the claims are considered as a whole, together with the prior art and appellants' disclosure, a person of ordinary skill in the art would understand what is claimed. Accordingly, we reverse the rejection of claims 12, 14, 15, 17, 19, 21, 23 and 25 under 35 U.S.C. § 112, second paragraph.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

While the examiner finds (Answer, page 5), appellants' disclosure enabling for the amino protecting group (R^4), "as a tert-butyl ester, tert-butyl carboxylate, or tert-butoxycarbonyl", the examiner finds (id.), "[t]he disclosure does not provide guidance as to what functional groups, and/or rings can be considered as an amino protecting group." Accordingly, the examiner concludes (id.), "one skilled in the art will have to carry out undue experimentation, as the chemical art is unpredictable."

In response, appellants argue (Brief, page 7), "[i]t is not necessary for an [a]pplicant to teach in the specification what is well-known in the art, and amino-protecting groups are well-known in the art." In support of this argument appellants rely on In re Fuetterer, 319 F.2d 259, 138 USPQ 217 (CCPA 1963), In re Robins, 429 F.2d 452, 166 USPQ 552 (CCPA 1970), In re Bowen, 492 F.2d 859, 181 USPQ 48 (CCPA 1974), and In re Skoll, 523 F.2d 1392, 187 USPQ

481 (CCPA 1975). However, according to the examiner (Answer, page 8), the "[c]ase laws [sic] cited by applicant are outdated. The most recent case law is (Genentech Inc. v. Novo Nordisk, 108 F.3d 1361, 42 USPQ 2d [sic] 1001 (Fed. Cir 1997)), in which the court ruled that relying on the knowledge of one skilled in the art cannot cure the deficiency in enablement." In this regard, the examiner asserts (id.), "[j]ust because a term is well-known in the art, it does not mean one skilled in the art can prepare any intermediate having any 'amino protecting group'." We will discuss each of the examiner's assertions in turn.

First, the examiner's assertion that Genentech stands for the proposition that "relying on the knowledge of one skilled in the art cannot cure the deficiency in enablement" is, on this record, erroneous. To the extent that the examiner is overly concerned about the publication date of case law, we note that on March 30, 2004 our appellant reviewing court rendered a decision in Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 70 USPQ2d 1321 (Fed. Cir. 2004). According to our appellate reviewing court (id. at 1254, 70 USPQ2d at 1325-26, alteration original),

> a patent disclosure need not enable information within the knowledge of an ordinarily skilled artisan. Thus, a patentee preferably omits from the disclosure any routine technology that is well known at the time of application. See Hybritech, 802 F.2d at 1384. At the other end of the knowledge continuum, a patent document cannot enable technology that arises after the date of application. The law does not expect an applicant to disclose knowledge invented or developed after the filing date. Such disclosure would be impossible. See In re Hogan, 559 F.2d 595, 605-06 [194 USPQ 527] (CCPA 1977). Nascent technology, however, must be enabled with a "specific and useful teaching." Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1368 [42 USPQ2d 1001] (Fed. Cir. 1997). The law requires an enabling disclosure for nascent technology because a person of ordinary

> skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology. See, e.g., J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc., 534 U.S. 124, 142 [60 USPQ2d 1865] (2001).

On this record, the examiner failed to provide any evidence that the claimed invention is directed to a nascent technology. To the contrary, the examiner did not dispute appellants' assertion (Brief, page 4) that "'amino protecting groups' are well-known and exemplified by many members, all of which are within the skill of the art of organic synthesis." Accordingly, contrary to the examiner's assertion Chiron reaffirms the well-established concept that "a patent disclosure need not enable information within the knowledge of an ordinarily skilled artisan. Thus, a patentee preferably omits from the disclosure any routine technology that is well known at the time of application."

Regarding the examiner's proffer that one skilled in the art would not be able to prepare "any intermediate having any 'amino protecting group'," we remind the examiner that "[w]hen rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "[It] is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of

any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

In our opinion, the examiner failed to meet his burden of establishing that appellants' disclosure does not enable the full scope of the claimed invention. The test for compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, is whether one skilled in the art would have to resort to undue experimentation in order to practice the invention as broadly as claimed. In considering this issue, we note that appellant is not required to disclose every parameter encompassed by the claims. See In re Angstadt, 537 F.2d 498, 503,190 USPQ 214, 218 (CCPA 1976). As set forth above, it is examiner's burden to show that one skilled in the art would have to resort to undue experimentation in order to practice the invention as broadly claimed. We are not persuaded by the examiner's reliance on In re Howarth, 654 F.2d 103, 107, 210 USPQ 689, 693 (CCPA 1981) in support of his assertion that appellant failed to "provide the starting material for R^4, nor a source for an 'amino protecting group'...." As Howarth, F.2d at 105, 210 USPQ at 691-92 recognizes, "a patent applicant need not include in the specification that which is already known to and available to the public." In our opinion, on this record, the examiner failed to meet his evidentiary burden of establishing that a person of ordinary skill in the art would not be able to practice the claimed invention without undue

experimentation. As set forth in Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984) "[t]he fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'"

Finally, we note that the examiner's rationale is internally inconsistent. First the examiner finds appellants' specification "enabling for R^4 as a tert-butyl ester, tert-butyl carboxylate, or tert-butoxycarbonyl..." yet later finds "undue experimentation is inevitable for one skilled in the art to make and use compounds with R^4 as a group other than tert.-butoxycarbonyl."

On reflection, it is our opinion that the examiner failed to meet his burden of establishing that appellants' disclosure does not enable the full scope of the claimed invention. Accordingly, we reverse the rejection of claims 12, 14, 15, 17, 19, 21, 23 and 25 under 35 U.S.C. § 112, first paragraph.

THE REJECTIONS UNDER 35 U.S.C. § 102:

Krogsgaard-Larsen:

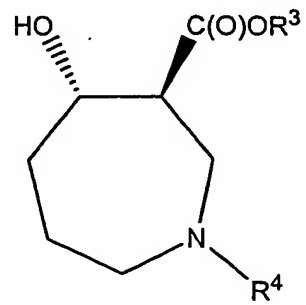
According to the examiner (Answer, page 9), "[c]ompounds 12 and 13 on page 328 [of Krogsgaard-Larsen] are embraced by formula VIII in claim 17 with R^3 as lower alkyl, and R^4[ ]as an amino protecting group." We will separately discuss the merits of the rejection as it relates to compounds 12 and 13.

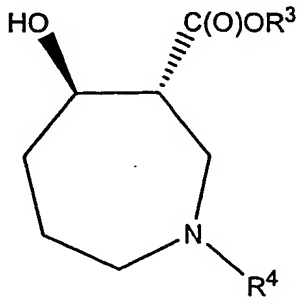
Compound 13

As appellants point out (Brief, page 8), "[c]ompound 13 of Krogsgaard-Larsen et al. has a trans configuration between the hydroxyl and ester groups ...

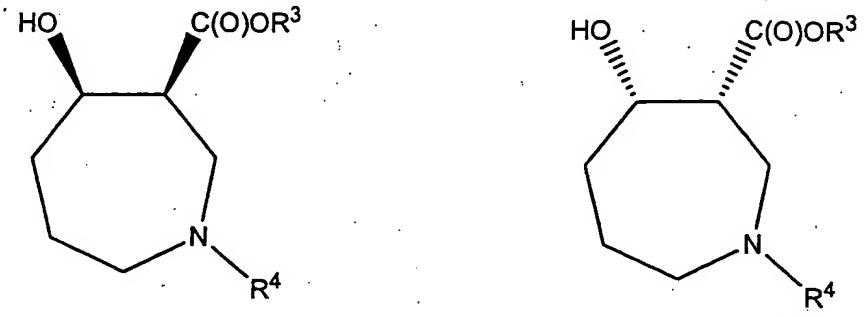
[and therefore] does not encompass the compounds of claim 17, which have a cis configuration between the hydroxyl and ester groups...." We agree.

We are not persuaded by the examiner's argument (Answer, page 10, emphasis removed), "spatial orientation of a compound can flip flop from one form to the other because bonds are not static." According to the examiner (id.), if a trans-form of a compound [exists], a cis-form also exists inevitably. This is the most fundamental principle in stereo-chemistry. So, if a reference discloses a trans-form, then a cis-form will be inherently embraced." The examiner's logic eludes us. The examiner fails to explain how one of ordinary skill in the art can isolate a particular enantiomeric form of a compound, as set forth in appellants' claimed invention, whose spatial orientation "flip flops" from one spatial orientation to another. Further, it appears that the examiner is confused with regard to "the most fundamental principles" of stereo-chemistry. The trans conformation of a molecule is not the stereoisomer of the cis conformation of a molecule. To the contrary, both the trans and the cis conformations of a molecule may each have two stereo-isomers, +/- trans and +/- cis. For example, for a trans molecule of the formula set forth in appellants' claim 17, the two enantiomers can be illustrated as follows:





In contrast, for a cis molecule of the formula set forth in appellants' claim 17, the two enantiomers can be illustrated as follows:



Note, as the examiner explains (Answer, bridging sentence, pages 10-11), with regard to compound 12, "both the –OH and the $-C(O)OCH_3$ can be pointed upward [▼] or downward [⋮], and still have [a] cis-configuration." These compounds which are nonsuperimposable mirror images of one another are called "enantiomers." As can be seen from the illustrations, cis-enantiomers differ from enantiomers in the trans-conformation.

Accordingly, as appellants point out (Brief, page 8), despite the examiner's assertions to the contrary, the trans confirmation of a molecule, as set forth in compound 13 of Krogsgaard-Larsen, cannot anticipate a specific enantiomeric form of the cis conformation of a molecule as set forth in appellants' claimed invention.

Compound 12

As the examiner recognizes (Brief, page 10, emphasis removed), "[t]he symbol, '(±)' [as it appears in the illustration of compound 12 of Krogsgaard-Larsen], refers to optical isomers of the cis-compound." Stated differently, compound 12 of Krogsgaard-Larsen refers to a racemic mixture containing both the "+" and the "–" enantiomers of the cis configuration of compound 12. As

appellants point out (Brief, page 9), "claim 17 excludes the racemic mixture disclosed [by Krogsgaard-Larsen] as compound 12." In this regard, we remind the examiner, as set forth in Akzo N.V., Aramide Maatschappij v.o.f. v. United States Int'l Trade Comm'n, 808 F.2d 1471, 1479, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), "[i]n addition to identity of invention, anticipation requires that a prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public." Here the examiner fails to explain how the racemic mixture of compound 12 taught by Krogsgaard-Larsen provides an enabling disclosure of the specific enantiomer set forth in appellants' claimed invention. See In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978), citing In re Williams, 171 F.2d 319, 80 USPQ 150 (1948), "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate."

For the foregoing reasons, we reverse the rejection of claim 17 under 35 U.S.C. § 102(b) as anticipated by Krogsgaard-Larsen.

Adams:

According to the examiner (Answer, page 9), "Formula X in [appellants'] claim 23 inherently embraces compound 20 on page 2356 [of Adams]. Formula XI in [appellants'] claim 25 inherently embraces compound 21 on page 2357 [of Adams]." However, as appellants point out (Brief, pages 7-8), the compound taught by Adams is in the trans-configuration, not the cis-configuration as required by appellants' claimed invention. To emphasize this "fundamental principle" of stereo-chemistry, we note that Adams resolve the enantiomers of compound 21. Scheme 3 on page 2357 of Adams, illustrates the two

enantiomeric forms (compound 21a and 21b) of the trans configuration of compound 21. See Adams, bridging sentence, page 2356, column 2 – page 2357, column 1; and Scheme 3, page 2357.

For the foregoing reasons, we reverse the rejection of claims 23 and 25 under 35 U.S.C. § 102(b) as anticipated by Adams.

Barbier:

According to the examiner (Answer, page 9), "Formula XI in [appellants'] claim 25 inherently embraces compounds B1-B23 listed on columns 18-21 [of Barbier]. However, as appellants point out (Brief, page 8), "[t]he exemplified compounds of Barbier et al. are all in the trans [con]formation."[4] Therefore, appellants assert (id.), "the teaching of the trans [con]formation does not anticipate the instantly claimed, structurally distinct, cis [con]formation."

Accordingly, we reverse the rejection of claim 25 under 35 U.S.C. § 102(e) as anticipated by Barbier.

THE REJECTION UNDER 35 U.S.C. § 103:

According to the examiner (Answer, page 11), Barbier "disclose a group of intermediates represented by formula III which resembles ... [appellants'] claimed formula XI...." From this the examiner asserts (id.), "[w]hile Barbier et al. do not disclose the cis-configuration of compounds of formula III or its species, such form is suggested in the racemic mixture of cis- and trans- represented by formula III." Accordingly, the examiner concludes (Answer, page 12), since

[4] We also note the examiner's statement (Answer, page 11), Barbier "do not disclose the cis-configuration of compounds of formula III or its species...."

> recognizes that substituents on the heterocylic ring can have [a] cis-configuration ... (see column 4, line 30) ... one of ordinary skill in the art would have been motivated to make the cis-configuration of compounds of formula III because such a configuration had been acknowledged by Barbier ... as an alternative to the trans-configuration.

According to the examiner (id.), "it is within the level of one skilled in the art to obtain the claimed cis-form from the teaching of Barbier et al., and conventional methods of resolving cis- and trans- forms."

Once again, we are compelled to point out that the trans conformation of a molecule is not the stereoisomer of the cis conformation of a molecule. Further, the burden is on the examiner to establish a prima facie case of obviousness of the claimed subject matter over prior art references. In re Deuel, 51 F.3d 1552, 1557, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995). Only after that burden is met must the applicant come forward with arguments or evidence in rebuttal. Id. Findings of fact must be supported by substantial evidence in the record. In re Gartside, 203 F.3d 1305, 1315, 53 USPQ2d 1769, 1775 (Fed. Cir. 2000). A rejection under §103 is proper only when "the PTO establishes that the invention as claimed in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations." In re Ochiai, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) (emphasis added).

On this record, the examiner fails to provide substantial evidence in support his assertion that "it is within the level of one skilled in the art to obtain the claimed cis-form from the teaching of Barbier et al., and conventional methods of resolving cis- and trans- forms." Emphasis added. At best, the

examiner appears to have relied on a per se rule that the specific stereoisomers set forth in appellants' claims 25 and 26 are obvious in view of a disclosure of the trans- and cis-isomers of the generic formula set forth on column 9 of Barbier. This is error. Ochiai at 1572, 37 USPQ2d at 1133 ("reliance on per se rules of obviousness is legally incorrect and must cease.").

We recognize, as set forth in In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995), that a prima facie case of obviousness based on structural similarity may arise if the "[s]tructural relations provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." Id. at 1558, 34 USPQ2d at 1214. See also, e.g., In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979) ("An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties."). However, as set forth in In re Doyle, 63 USPQ2d 1161, 1162 (Fed. Cir. 2002), footnote omitted,

> Like a human hand, a chiral molecule cannot be superimposed on its mirror image, otherwise known as its enantiomer. Altering the relative orientation of the groups bonded to the various chiral centers of a molecule (i.e., creating a different stereoisomer of the compound) can have profound effects on the compound's properties, especially with respect to how the compound interacts with other chiral molecules.

Thus, assuming arguendo that it would have been prima facie obvious to a person of ordinary skill in the art to separate the cis- and trans-conformations of a compound of formula III in Barbier, the examiner failed to identify any evidence that it would have been prima facie obvious to then separate the + and – stereoisomers of the cis-conformation to arrive at appellants' claimed invention. Accordingly, we reverse the rejection of claims 25 and 26 under 35 U.S.C. § 103 as being unpatentable over Barbier.

REVERSED

Sherman D. Winters
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

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41 6,936,597 Prodrugs of anticancer agents employing substituted aromatic acids
42 6,933,403 Mono carbonylation of benzene diols
43 6,933,396 Process to prepare psorospermin
44 6,933,295 Substituted isoindoles and the use thereof
45 6,930,185 Melanin-concentrating hormone antagonist
46 6,930,179 Method for the trichromatic dyeing or printing of synthetic polyamide fiber materials
47 6,930,110 Substituted alkylaminopyridazinone derivatives, process for the preparation thereof and pharmaceutical composition containing the same
48 6,927,300 Process for the preparation of Latanoprost
49 6,927,291 Method for the synthesis of 2',3'-dideoxy-2',3'-didehydronucleosides
50 6,927,230 Triazole derivatives

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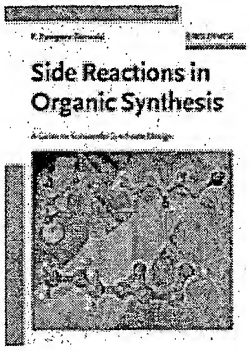
Side Reactions in Organic Synthesis



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Florencio Zaragoza Dörwald

Softcover, 374 Pages
First Edition, 2004
ISBN: 3-527-31021-5 - Wiley-VCH

Description

Most syntheses in the chemical research laboratory fail and usually require several attempts before proceeding satisfactorily. Failed syntheses are not only discouraging and frustrating, but also cost a lot of time and money. Many failures may, however, be avoided by understanding the structure-reactivity relationship of organic compounds.

This textbook highlights the competing processes and limitations of the most important reactions used in organic synthesis. By allowing chemists to quickly recognize potential problems this book will help to improve their efficiency and success-rate. A must for every graduate student but also for every chemist in industry and academia.

Editorial Review

There are several reactions in organic chemistry that come up time and again. Combinatorial chemistry and drug development work is often based on a small basis set of well-optimized, versatile synthetic methods, such as alkylation, acylation, and palladium-catalyzed cross-coupling, which can be applied to a broad range of reactants. In principle, the goal is to find the best available method within the limitations of selectivity (in multifunctional molecules) and reactivity (in sterically hindered molecules), but there is often not enough time to optimize individual transformations.

The monograph "Side Reactions in Organic Synthesis" focuses on a small number of reactions, which are explained through case studies of how the transformation can go awry. This work can readily be used as a textbook, since it combines theoretical explanations with concrete examples to help solidify the reader's understanding. It can also serve as a guidebook for those situations where a standard method simply fails in the laboratory.

"Side Reactions in Organic Synthesis" will appeal both to advanced students who wish to revisit the underlying concepts, as well as to practitioners who need to find a quick alternative when a problem arises. The book is quite pithy, and the selection of subjects and chapters has resulted in a rather successful contribution.

Meinung der Redaktion

Es gibt einige Reaktionen in der Organischen Chemie, auf die man häufiger trifft. Kombinatorische Chemie und Wirkstoff-Entwicklung beruhen oftmals nur auf einem kleinen Basis-Set an gut-optimierten, versatilen Synthese-Methoden - wie Alkylierungen, Acylierungen und Palladium-katalysierte Kreuzkupplungen - die für eine grosse Bandbreite an Edukten zum Einsatz kommen. Im Prinzip müsste innerhalb der Grenzen von Selektivität (bei mehrfachfunktionalisierten Molekülen) und Reaktitivität (bei sterisch gehinderten Molekülen) die beste Methode gefunden werden, doch vielmals fehlt die Zeit, um einzelne Umsetzungen zu optimieren.

"Side Reactions in Organic Synthesis" beschränkt sich auf ein kleine Zahl von Reaktionen, erläutert aber anhand von Fallbeispielen Variationsmöglichkeiten. Das Buch kann durchaus als Lehrbuch dienen, da es mit einigen theoretischen Erläuterungen und konkreten Beispielen hilft, Wissen zu verknüpfen. Es kann aber auch als Ratgeber in Situationen herhalten, in denen eine Standardmethode im Labor versagt.

Fortgeschrittene Studenten, welche sich noch einmal vertiefend mit grundlegenden Konzepten befassen wollen, aber auch Anwender, welche eine schnelle Idee für eine Alternative benötigen, werden Gefallen an "Side Reactions in Organic Synthesis" finden. Das Buch ist zwar kompakt, die Auswahl der Themen und Kapitel ist aber durchaus gelungen.

Contents

>> Description

O=CHem

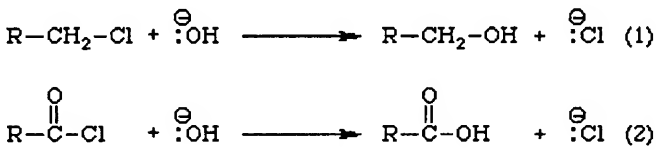
Derivatives of Carboxylic Acids

Introduction

The discussion of carboxylic acids, introduced the members of the carboxylic acid family; carboxylic acids, esters, amides, anhydrides, and acyl halides. This topic looks at the latter four members of this family, with an emphasis on the formation of esters and amides.

Nucleophilic Acyl Substitution Reactions

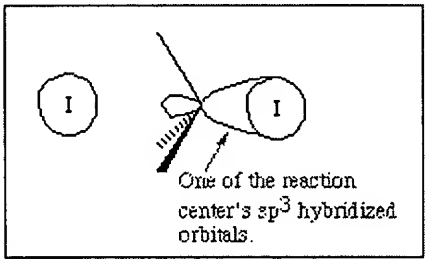
Consider for a moment, the reactions outlined in Equations 1 and 2.



In our discussion of nucleophilic aliphatic substitution reactions we considered the experimental evidence that led to the formulation of the mechanism for reaction 1. Figure 1 reiterates that mechanism using iodide ion as both the nucleophile and the leaving group.

Figure 1

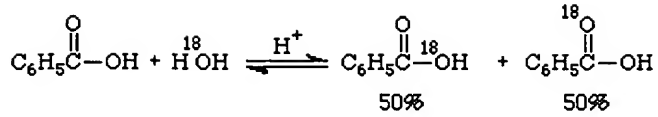
The Sn2 Mechanism



At first glance it seems reasonable to assume that reaction 2 proceeds by this same mechanism. However, the experimental results of the isotopic labeling study shown in Figure 2 show clearly that this assumption is false.

Figure 2

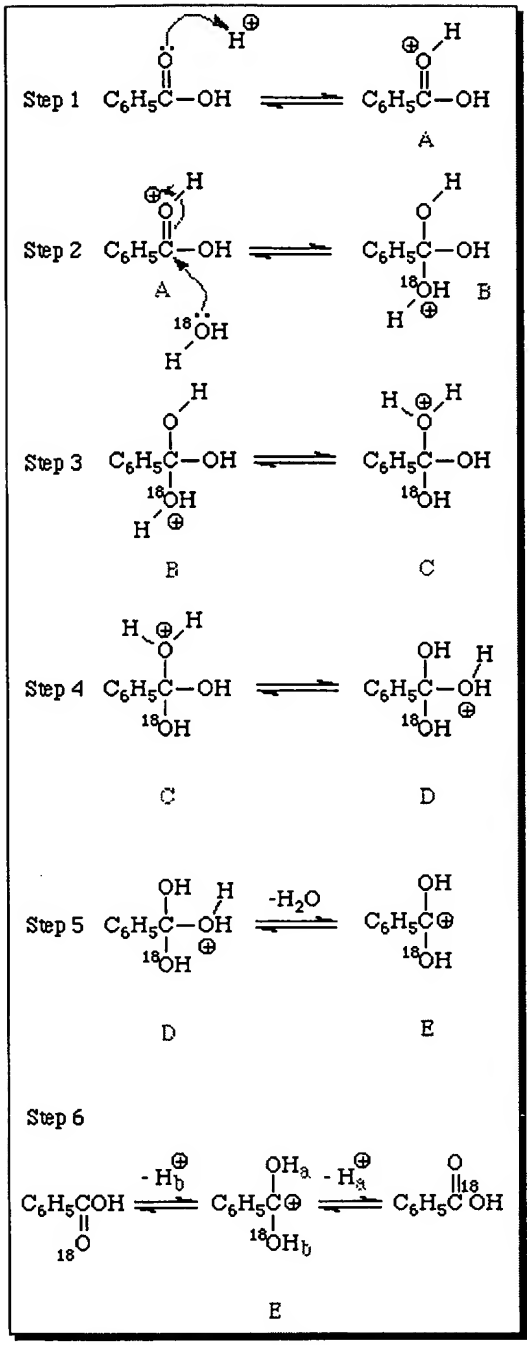
An Isotopic Exchange Experiment



If the reaction outlined in Figure 2 involved direct displacement of a (protonated) OH group by an isotopically labeled water molecule, then all of the label should end up in the acyl oxygen. Mass spectral analysis indicates that half of the label ends up in the acyl oxygen, while the other half is found in the carbonyl oxygen. This 50/50 distribution suggests that a symmetrical intermediate is involved in this reaction. Scheme 1 indicates how such an intermediate might be formed.

Scheme 1

Rationalizing Results



According to this scheme, the benzoic acid is activated toward nucleophilic attack by protonation of the carbonyl oxygen. This preliminary equilibrium generates oxonium ion A. In the second step, addition of a labeled water molecule to the carbonyl carbon produces the tetrahedral intermediate B. A series of proton transfers, steps 3 and 4, scrambles the label between all three oxygen atoms. Note that intermediates B, C, and D are identical except for the isotopic label. Loss of a molecule of water, step 5, produces an intermediate, resonance-stabilized, carbocation, E, in which the two OH groups are indistinguishable except for the label. In step 6, loss of a proton from either OH group, followed by reformation of the C-O double bond regenerates the benzoic acid. Since the probability of losing H_a is identical to that of losing H_b, the ^{18}O label is evenly distributed between the two oxygen atoms of the equilibrated benzoic acid.

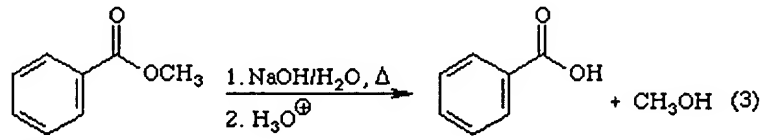
Exercise 1 Draw resonance structures for intermediate E in Scheme 1.

Exercise 2 How many valid resonance structures are there for intermediate E? [ ]

A key feature of the reactions shown in Scheme 1 and of nucleophilic acyl substitution reactions in general is the formation of a tetrahedral intermediate by addition of a nucleophile to the carbonyl carbon. This step is the rate determining step in all nucleophilic acyl substitution reactions. It is analogous to the first step in the nucleophilic addition reactions of aldehydes and ketones. We will consider the alternative fates of the tetrahedral intermediates involved in these two pathways shortly. First however, let's take a look at a nucleophilic acyl substitution reaction of major biological importance, namely saponification of esters.

Saponification of Esters

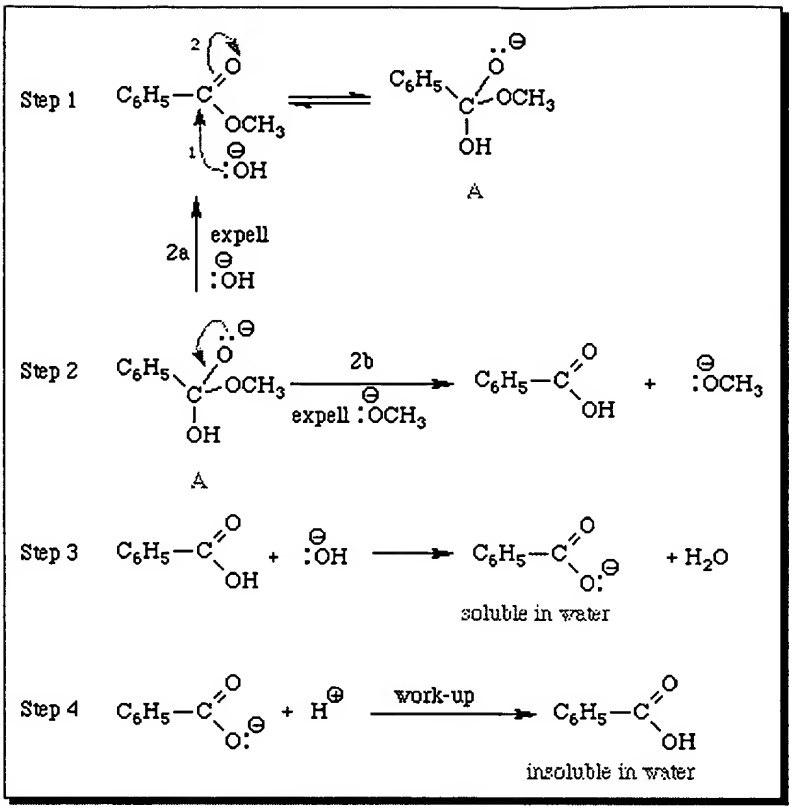
When methyl benzoate is refluxed with a concentrated solution of sodium hydroxide, the initially heterogeneous mixture slowly becomes homogeneous. Work-up of the reaction mixture by acidification with strong acid yields a white precipitate of benzoic acid in high yield. Equation 3 illustrates the overall reaction, while Scheme 2 outlines the sequence of transformations step-by-step.



methyl benzoate

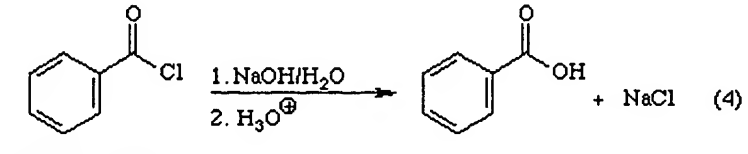
Scheme 2

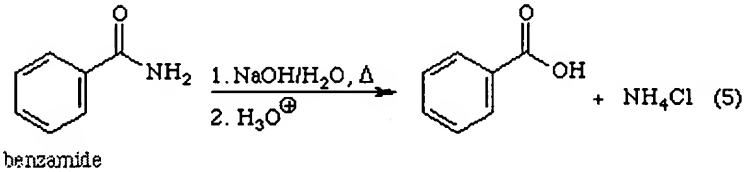
Saponification of an Ester

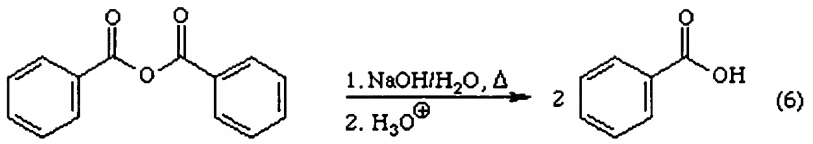


The reaction begins with addition of a hydroxide ion to the carbonyl carbon of the ester. This generates tetrahedral intermediate A. Regeneration of the carbonyl group in Step 2 leads to the expulsion of either the OH group that bonded to the carbonyl carbon originally (Step 2a) or to expulsion of the methoxy group (Step 2b). The former event regenerates the starting materials, while the latter produces a molecule of benzoic acid, which, in the strongly basic solution is immediately deprotonated (Step 3). The resulting sodium benzoate, being ionic, is soluble in the aqueous solution. However, protonation of the benzoate ion yields benzoic acid which is much less soluble and which precipitates from the reaction mixture.

The mechanism outlined in Scheme 2 is quite general. Esters, amides, acid halides, and anhydrides all undergo nucleophilic acyl substitution reactions by this mechanism. Consider the reactions shown in Equations 4-6.



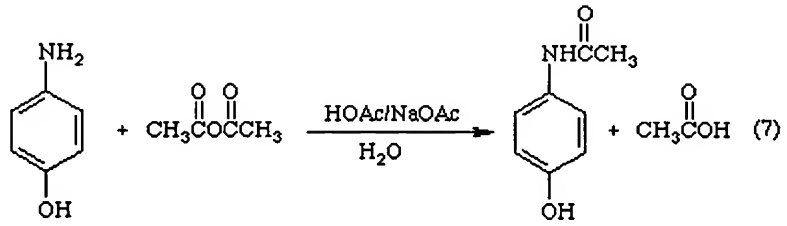




benzoic anhydride

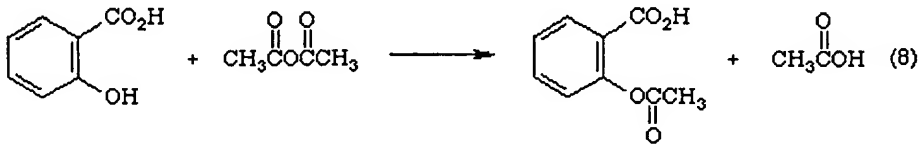
In each case, the reaction begins with the addition of hydroxide ion to the acyl group, which produces a tetrahedral intermediate. Regeneration of the carbonyl group is accompanied by expulsion of the leaving group, either chloride ion, amide ion, or benzoate ion. The relative stabilities of these leaving groups determines the relative rates at which the starting materials react. The relative stabilities of the leaving groups is easily assessed by comparing the pKa values of their conjugate acids, which, in the case of reactions 3-6 are CH_3OH (pKa=16), HCl (pKa = -7), NH_3 (pKa = 38), and $C_6H_5CO_2H$ (pKa = 5). This means that chloride ion is the best leaving group, while amide ion is the worst. In other words, acid halides are more reactive than anhydrides, which are more reactive than esters, which are more reactive than amides towards nucleophilic aliphatic substitution. We can push the use of pKa values a bit further and say that acid chlorides are approximately 10^{12} times as reactive as anhydrides; anhydrides are around 10^{11} times more reactive than esters; esters are about 10^{12} times as reactive as amides. What this means is that running reaction 4 is a risky proposition; the reaction would be extremely exothermic, perhaps even causing the reactants to boil out of the flask. On the other hand, you should expect reaction 5 to require an extended period of heating before all of the benzamide reacts.

As mentioned earlier, acid halides and anhydrides are generally not synthetic targets. Rather they are used to prepare esters and amides. Equations 7-10 offer some typical examples.

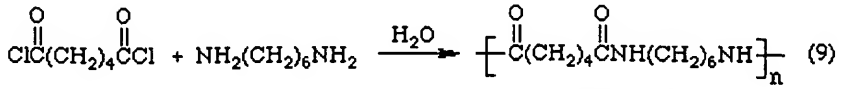


Acetaminophen

In this reaction a buffer of acetic acid and sodium acetate keeps the pH high enough to insure that the 4-aminophenol is not completely protonated by the acetic acid that is formed as a side product. If the buffer were omitted, the acetic acid generated in the reaction could protonate unreacted 4-aminophenol, rendering it non-nucleophilic.

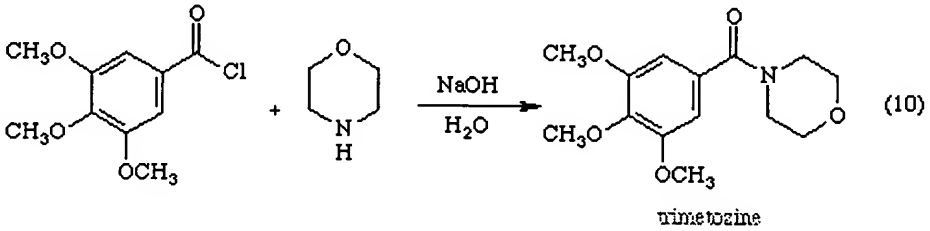


Acetyl salicylic acid (aspirin)



nylon [6,6]

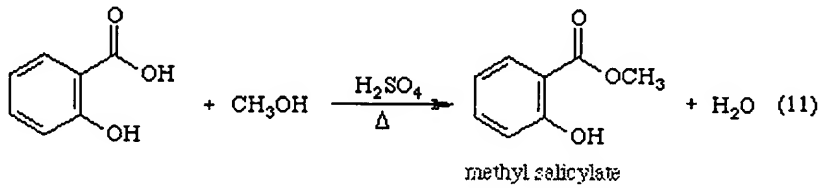
The reaction of the diacid chloride, sebacoyl chloride, with the diamine, hexmethylenediamine, results in nucleophilic acyl substitution at both ends of both molecules. The product is the well known polyamide nylon[6,6], where the symbol [6,6] indicates the number of carbons in the diacid chloride and the diamine. Nylons with different repeat units are easily prepared by variations on the reaction shown in Equation 9.



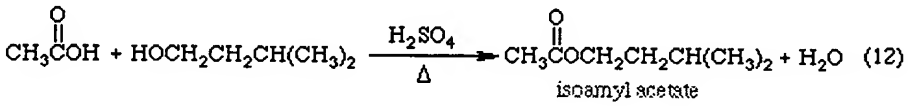
In this reaction the NaOH acts as an acid trap, neutralizing the HCl that is formed as a side product. The product of the reaction, trimetozine, is sometimes used as a sedative.

Note that in all of these reactions the nucleophilic may be described as ROH, RNH_2, or R_2NH. Whenever the nucleophile is electrically neutral, the nucleophilic atom must have an H attached to it in order for the substitution to be productive. Ultimately that H ends up combined with the leaving group as HCl or HOAc, etc. Thus, while ethers, ROR, and tertiary amines, R_3N, both contain nucleophilic atoms, they do not react in a productive manner.

While it is possible to prepare esters from acid halides or anhydrides, the more common approach involves the direct, acid catalysed reaction of carboxylic acids with alcohols. A specific example is the esterification of salicylic acid with methanol to produce methyl salicylate, one of the major components in oil of wintergreen, as shown in Equation 11.



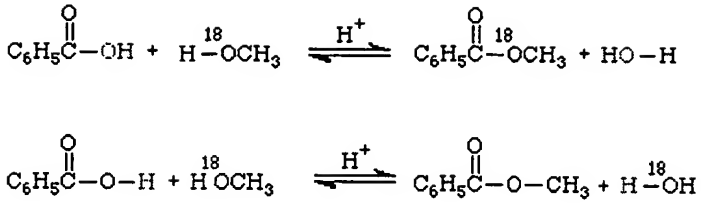
Many esters are fragrant compounds. For example, isoamyl acetate, which may be synthesized by the reaction of acetic acid with isoamyl alcohol as outlined in Equation 12, smells like bananas. It is also a component of the alarm pheromone of honeybees.



An interesting question involving esterification reactions like 11 and 12 involves the identities of the oxygen atoms in the reactants and products. In other words, does the OH group of the water come from the alcohol or from the carboxylic acid? The experiment outlined in Figure 3 provided the answer to this question.

Figure 3

Another Isotopic Exchange Experiment



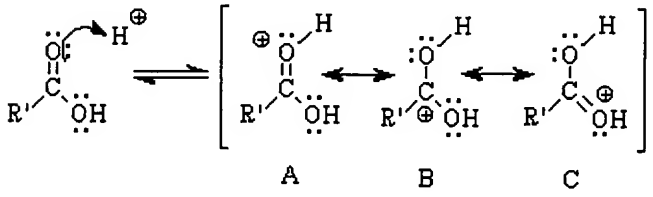
Here the benzoic acid was mixed with isotopically labeled methanol. If methanol acts as the nucleophile, displacing (protonated) OH from the carbonyl group the first alternative should be observed. If the acyl oxygen atom acts as a nucleophile, displacing (protonated) OH from the methyl group, then the second outcome should obtain. Analysis of the methyl benzoate and water formed in the reaction revealed that all of the ^{18}O was present in the methyl benzoate and none of it was in the water.

Although they involve an acid catalyst, esterification reactions like 11 and 12 are still nucleophilic acyl substitution reactions. The mechanism of acid catalysed esterification is similar to that outlined in Scheme 2 except that the process begins with protonation of a carbonyl oxygen atom. Scheme 3 summarizes the steps required to transform the reactants to products.

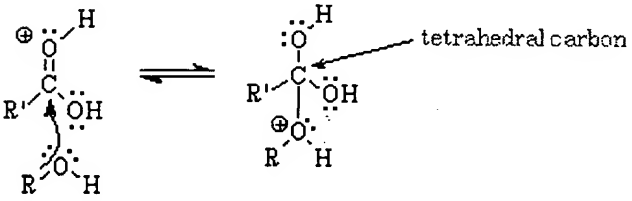
Scheme 3

Acid Catalysed Esterification

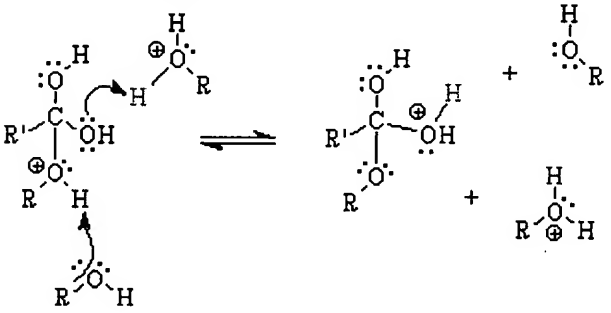
Step 1- Protonation of the carbonyl oxygen atom produces a resonance stabilized intermediate which is reactive towards nucleophiles.



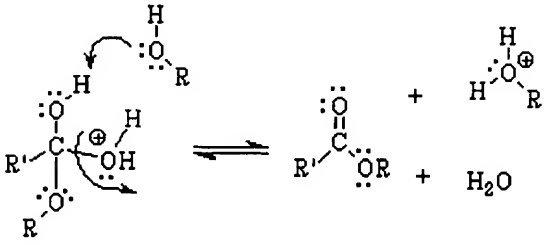
Step 2- The positive charge in the intermediate attracts an alcohol molecule, leading to the formation of a bond between the carbonyl carbon and an oxygen atom. A tetrahedral intermediate is formed.



Step 3- Under the reaction conditions, solvent molecules readily transfer protons from one oxygen atom to another.



Step 4- The intermediate produced in Step 3 undergoes a dehydration reaction. This is a typical reaction of protonated alcohols.

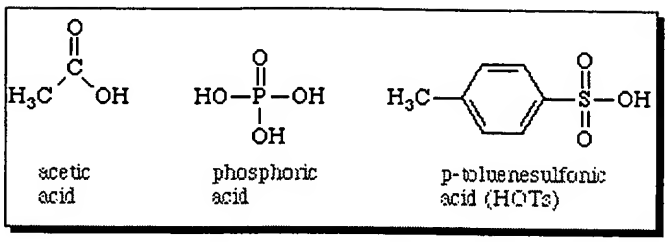


Extensions

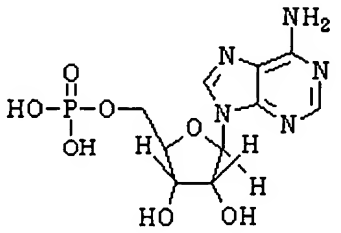
Carboxylic acids are not the only kinds of acids that react with alcohols to produce esters. Phosphoric acid and sulfonic acids behave similarly to produce phosphate esters and sulfonate esters. Figure 4 compares the structures of these three types of acids.

Figure 4

A Comparison of Different Types of Acids



Esterification is not limited to carboxylic acids. Alcohols react with phosphoric acid to produce phosphate esters, which are important components of nucleic acids. Adensosine monophospahte (AMP) is an important phosphate ester in biological systems.

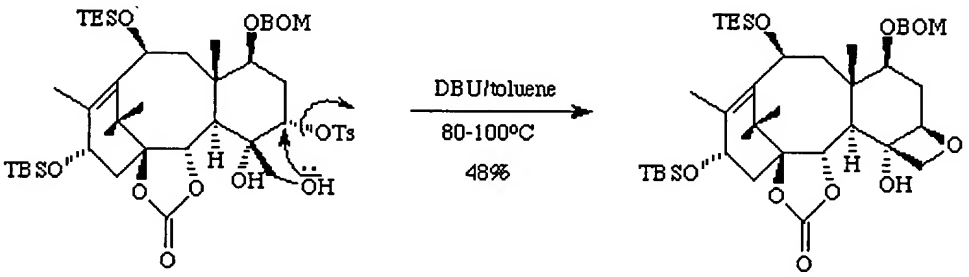


Adenosine monophosphate

Sulfonate esters are useful intermediates in organic synthesis. Figure 5 illustrates a key step in one of the first total syntheses of (-)-taxol, a natural product that is used in the treatment of ovarian cancer. The reaction involves an intramolecular nucleophilic substitution in which a primary alcohol displaces a sulfonate ester of p-toluenesulfonic acid. The tosylate group was introduced into the molecule by esterification of an alcohol in an earlier step in the synthesis.

Figure 5

The Use of a Sulfonate Ester in Organic Synthesis



O=CHem Directory